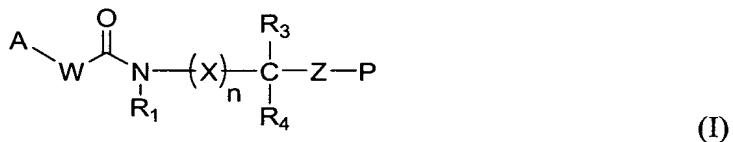


AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions of the claims and listing of the claims in the application:

1. (Currently Amended) A compound of Formula I,



wherein

A is a Met-AP2 inhibitory core;

W is O or NR₂;

R₁ and R₂ are each, independently, hydrogen or alkyl;

X is alkylene or substituted alkylene;

n is 0 or 1;

R₃ and R₄ are each, independently, substituted alkyl, substituted aryl or substituted or unsubstituted heteroaryl; or R₃ and R₄, together with the carbon atom to which they are attached, form a carbocyclic or heterocyclic group; or R₃ and R₄ together form an alkylene group;

Z is -C(O)-, alkylene or alkylene-C(O)-; and

P is a peptide comprising from 1 to about 100 amino acid residues attached at its amino terminus to Z or a group OR₅ or N(R₆)R₇, wherein

R₅, R₆ and R₇ are each, independently, hydrogen, alkyl, substituted alkyl, azacycloalkyl or substituted azacycloalkyl; or R₆ and R₇, together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocyclic ring structure;

or

Z is -O-, -NR₈-, alkylene-O- or alkylene-NR₈-, where R₈ is hydrogen or alkyl; and

P is hydrogen or a peptide consisting of from 1 to about 100 amino acid residues attached at its carboxy terminus to Z; wherein

the N-terminus of the peptide is -NR₂R₃ -NR₂R₃, wherein R₂R₂ is hydrogen, alkyl or arylalkyl and R₃R₃ is hydrogen, alkyl, arylalkyl or acyl.

2. (Currently Amended) The compound of claim 1, wherein at least one of R_4 , R_3 and R_4 is a substituted or unsubstituted alkyl group.

3. (Currently Amended) The compound of claim 2, wherein at least one of R_4 , R_3 and R_4 is a substituted or unsubstituted normal, branched or cyclic C_1 - C_6 alkyl group.

4. (Currently Amended) The compound of claim 3, wherein at least one of R_4 , R_3 and R_4 is a normal or branched C_1 - C_4 alkyl group.

5. (Currently Amended) The compound of claim 1, wherein one of R_3 and R_4 is a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted heteroarylalkyl group, or a substituted or unsubstituted arylalkyl group.

6. (Currently Amended) The compound of claim 5, wherein one of R_3 and R_4 is selected from the group consisting of phenyl, naphthyl, indolyl, imidazolyl, pyridyl, benzyl, naphthylmethyl, indolylmethyl, imidazolylmethyl and pyridylmethyl.

7. (Original) The compound of claim 1, wherein n is 1 and X is C_1 - C_6 -alkylene.

8. (Original) The compound of claim 7, wherein X is methylene or ethylene.

9. (Original) The compound of claim 1, wherein Z is C_1 - C_6 -alkylene- $C(O)$ -.

10. (Original) The compound of claim 9, wherein Z is methylene- $C(O)$ - or ethylene- $C(O)$ -.

11. (Previously Presented) The compound of claim 1, wherein at least one of R_6 and R_7 is alkyl, substituted alkyl, substituted or unsubstituted azacycloalkyl or substituted or unsubstituted azacycloalkylalkyl.

12. (Original) The compound of claim 11, wherein at least one of R₆ and R₇ is an azacycloalkyl group having an N-alkyl substituent.

13. (Original) The compound of claim 12, wherein the N-alkyl substituent is a C₁-C₄-alkyl group.

14. (Original) The compound of claim 13, wherein the N-alkyl substituent is a methyl group.

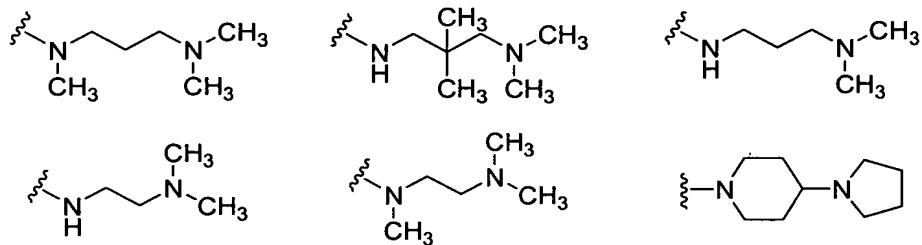
15. (Original) The compound of claim 1, wherein R₆ and R₇, together with the nitrogen atom to which they are attached, form a substituted or unsubstituted five or six-membered aza- or diazacycloalkyl group.

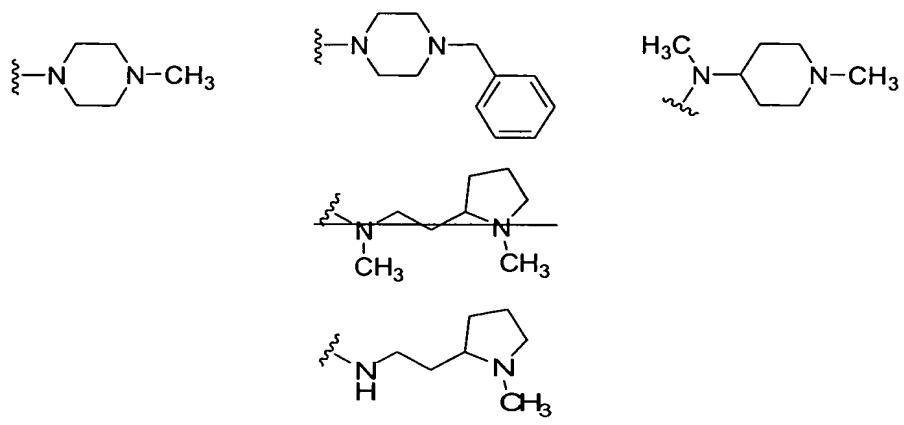
16. (Original) The compound of claim 15, wherein R₆ and R₇, together with the nitrogen atom to which they are attached, form a substituted or unsubstituted five or six-membered diazacycloalkyl group which includes an N-alkyl substituent.

17. (Original) The compound of claim 16, wherein the N-alkyl substituent is a C₁-C₄-alkyl group.

18. (Original) The compound of claim 17, wherein the N-alkyl substituent is a methyl group.

19. (Currently Amended) The compound of claim 1, wherein P is NH₂ or one of the groups shown below:





20. (Currently Amended)

A compound of Formula XV,



wherein

A is a MetAP-2 inhibitory core;

W is O or NR;

each R is, independently, hydrogen or alkyl;

Z is $-\text{C}(\text{O})-$ or $-\text{alkylene-C}(\text{O})-$;

P is NHR, OR or a peptide consisting of one to about one hundred amino acid residues connected at the N-terminus to Z;

Q is hydrogen, linear, branched or cyclic alkyl or aryl, provided that when P is $-\text{OR}$, Q is not hydrogen;

or

Z is $-\text{alkylene-O-}$ or $-\text{alkylene-N(R)-}$;

P is hydrogen or a peptide consisting of from one to about one hundred amino acid residues connected to Z at the carboxyl terminus; wherein

the N-terminus of the peptide is $-\text{NR}_2\text{R}_3$ $-\text{NR}_2\text{R}_3$, wherein R_2 - R_2 is hydrogen, alkyl or arylalkyl and R_3 R_3 is hydrogen, alkyl, arylalkyl or acyl.

Q is hydrogen, linear, branched or cyclic alkyl or aryl, provided that when P is hydrogen, Q is not hydrogen;
and pharmaceutically acceptable salts thereof.

21. (Previously Presented) The compound of claim 20, wherein Z is $-\text{C}(\text{O})-$ or $\text{C}_1\text{-C}_4\text{-alkylene-C}(\text{O})-$.

22. (Original) The compound of claim 21, wherein Z is $-\text{C}(\text{O})-$ or $\text{C}_1\text{-C}_2\text{-alkylene-C}(\text{O})-$.

23. (Cancelled)

24. (Cancelled)

25. (Previously Presented) The compound of claim 20, wherein Z is $\text{C}_1\text{-C}_6\text{-alkylene-O-}$ or $\text{C}_1\text{-C}_6\text{-alkylene-NR-}$.

26. (Original) The compound of claim 25, wherein Z is $\text{C}_1\text{-C}_4\text{-alkylene-O-}$ or $\text{C}_1\text{-C}_4\text{-alkylene-NH-}$.

27. (Original) The compound of claim 26, wherein Z is $\text{C}_1\text{-C}_2\text{-alkylene-O-}$ or $\text{C}_1\text{-C}_2\text{-alkylene-NH-}$.

28. (Currently Amended) The compound of claim 25, wherein Q is hydrogen, linear, branched or cyclic $\text{C}_1\text{-C}_6\text{-alkyl}$, phenyl or naphthyl, provided that when P is hydrogen or $-\text{OR}$, Q is not hydrogen.

29. (Original) The compound of claim 28, wherein Q is isopropyl, phenyl or cyclohexyl.

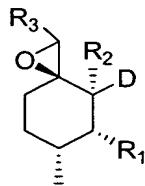
30. (Original) The compound of claim 20, wherein each R is, independently, hydrogen or linear, branched or cyclic $\text{C}_1\text{-C}_6\text{-alkyl}$.

31. (Original) The compound of claim 30, wherein each R is, independently, hydrogen or linear or branched C₁-C₄-alkyl.

32. (Original) The compound of claim 31, wherein each R is, independently, hydrogen or methyl.

33. (Original) The compound of claim 32, wherein each R is hydrogen.

34. (Previously Presented) The compound of claim 20, wherein A is of Formula II,



(II)

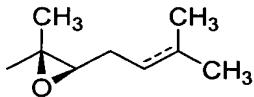
wherein

R₁ is hydrogen or alkoxy;

R₂ is hydrogen or hydroxy;

R₃ is hydrogen or alkyl; and

D is linear or branched alkyl or arylalkyl; or D is of the structure



35. (Original) The compound of claim 34, wherein R₁ is C₁-C₄-alkoxy.

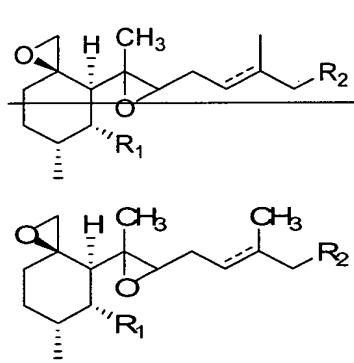
36. (Original) The compound of claim 35, wherein R₁ is methoxy.

37. (Original) The compound of claim 34, wherein R₃ is hydrogen or C₁-C₄-alkyl.

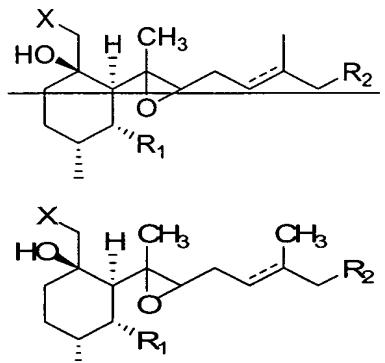
38. (Original) The compound of claim 37, wherein R₃ is methyl.

39. (Previously Presented) The compound of claim 34, wherein D is linear, or branched C₁-C₆-alkyl; or aryl-C₁-C₄-alkyl.

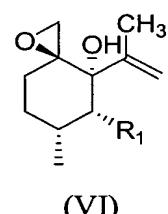
40. (Previously Presented) The compound of claim 20, wherein A is selected from the group consisting of



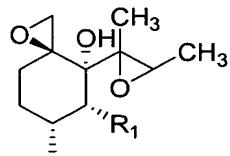
(IV)



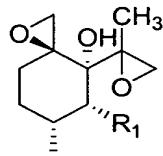
(V)



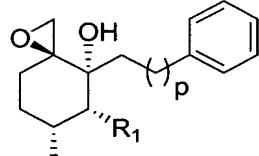
(VI)



(VII)



(VIII)



(IX)

wherein

p is an integer from 0 to 10;

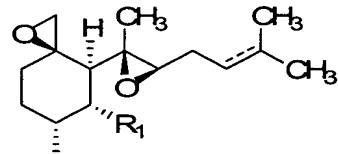
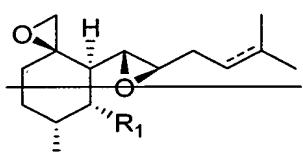
R₁ is hydrogen, -OH or C₁-C₄-alkoxy;

X is a leaving group; and

R₂ is H, OH, amino, C₁-C₄-alkylamino or di(C₁-C₄)-alkylamino.

41. (Currently Amended)

The compound of claim 40, wherein A is of the formula



42. (Original) The compound of claim 20, wherein P comprises from 1 to about 20 amino acid residues.

43. (Original) The compound of claim 42, wherein P comprises an amino acid sequence which is a substrate for a matrix metalloprotease.

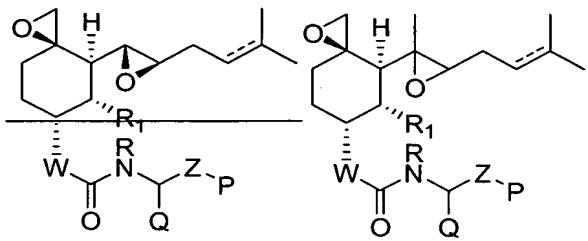
44. (Original) The compound of claim 43, wherein the matrix metalloprotease is selected from the group consisting of MMP-2, MMP-1, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13 and MMP-26.

45. (Original) The compound of claim 44, wherein the matrix metalloprotease is MMP-2 or MMP-9.

46. (Original) The compound of claim 45, wherein P comprises the sequence -Pro-Leu-Gly-Xaa-, wherein Xaa is a naturally occurring amino acid residue.

47. (Currently Amended) The compound of claim 46, wherein P comprises a the sequence selected from the group consisting of Pro-Cha-Gly-Cys(Me)-His (SEQ ID NO:2); Pro-Gln-Gly-Ile-Ala-Gly-Gln-D-Arg (SEQ ID NO:3); Pro-Gln-Gly-Ile-Ala-Gly-Trp (SEQ ID NO:4); Pro-Leu-Gly-Cys(Me)-His-Ala-D-Arg (SEQ ID NO:5); Pro-Leu-Gly-Met-Trp-Ser-Arg (SEQ ID NO:35); Pro-Leu-Gly-Leu-Trp-Ala-D-Arg (SEQ ID NO:6); Pro-Leu-Ala-Leu-Trp-Ala-Arg (SEQ ID NO:7); Pro-Leu-Ala-Leu-Trp-Ala-Arg (SEQ ID NO:8); Pro-Leu-Ala-Tyr-Trp-Ala-Arg (SEQ ID NO:9); Pro-Tyr-Ala-Tyr-Trp-Met-Arg (SEQ ID NO:10); Pro-Cha-Gly-Nva-His-Ala (SEQ ID NO:11); Pro-Leu-Ala-Nva (SEQ ID NO:12); Pro-Leu-Gly-Leu (SEQ ID NO:13); Pro-Leu-Gly-Ala (SEQ ID NO:14); Arg-Pro-Leu-Ala-Leu-Trp-Arg-Ser (SEQ ID NO:15); Pro-Cha-Ala-Abu-Cys(Me)-His-Ala (SEQ ID NO:16); Pro-Cha-Ala-Gly-Cys(Me)-His-Ala (SEQ ID NO:17); Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu (SEQ ID NO:18); Pro-Lys-Pro-Leu-Ala-Leu (SEQ ID NO:19); Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met (SEQ ID NO:20); Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg (SEQ ID NO:21); Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg (SEQ ID NO:22); and Arg-Pro-Lys-Pro-Leu-Ala-Nva-Trp (SEQ ID NO:23).

48. (Currently Amended) A compound of the formula



wherein

W is O or NR;

each R is, independently hydrogen or a C₁-C₄-alkyl;

Q is hydrogen, linear, branched or cyclic C₁-C₆-alkyl, or aryl;

R₁ is hydroxy, C₁-C₄-alkoxy or halogen;

Z is -C(O)- or C₁-C₄-alkylene-C(O)-;

P is ~~NHR, OR, or a peptide comprising 1 to 100 amino acid residues attached to Z at the N-terminus; or~~

Z is alkylene-O or alkylene-NR; and

P is ~~hydrogen or a peptide comprising 1 to 100 amino acid residues attached to Z at the C-terminus;~~

~~or a pharmaceutically acceptable salt thereof, provided that when P is hydrogen, NHR or OR, Q is not hydrogen.~~

49. (Cancelled)

50. (Cancelled)

51. (Original) The compound of claim 48, wherein P comprises from 1 to about 20 amino acid residues.

52. (Original) The compound of claim 51, wherein P comprises an amino acid sequence which is a substrate for a matrix metalloprotease.

53. (Original) The compound of claim 52, wherein the matrix metalloprotease is selected from the group consisting of MMP-2, MMP-1, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13 and MMP-26.

54. (Original) The compound of claim 53, wherein the matrix metalloprotease is MMP-2 or MMP-9.

55. (Original) The compound of claim 54, wherein P comprises the sequence -Pro-Leu-Gly-Xaa-, wherein Xaa is a naturally occurring amino acid residue.

56. (Currently Amended) The compound of claim 55, wherein P comprises a the sequence selected from the group consisting of Pro-Cha-Gly-Cys(Me)-His (SEQ ID NO:2); Pro-Gln-Gly-Ile-Ala-Gly-Gln-D-Arg (SEQ ID NO:3); Pro-Gln-Gly-Ile-Ala-Gly-Trp (SEQ ID NO:4); Pro-Leu-Gly-Cys(Me)-His-Ala-D-Arg (SEQ ID NO:5); Pro-Leu-Gly-Met-Trp-Ser-Arg (SEQ ID NO:35); Pro-Leu-Gly-Leu-Trp-Ala-D-Arg (SEQ ID NO:6); Pro-Leu-Ala-Leu-Trp-Ala-Arg (SEQ ID NO:7); Pro-Leu-Ala-Leu-Trp-Ala-Arg (SEQ ID NO:8); Pro-Leu-Ala-Tyr-Trp-Ala-Arg (SEQ ID NO:9); Pro-Tyr-Ala-Tyr-Trp-Met-Arg (SEQ ID NO:10); Pro-Cha-Gly-Nva-His-Ala (SEQ ID NO:11); Pro-Leu-Ala-Nva (SEQ ID NO:12); Pro-Leu-Gly-Leu (SEQ ID NO:13); Pro-Leu-Gly-Ala (SEQ ID NO:14); Arg-Pro-Leu-Ala-Leu-Trp-Arg-Ser (SEQ ID NO:15); Pro-Cha-Ala-Abu-Cys(Me)-His-Ala (SEQ ID NO:16); Pro-Cha-Ala-Gly-Cys(Me)-His-Ala (SEQ ID NO:17); Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu (SEQ ID NO:18); Pro-Lys-Pro-Leu-Ala-Leu (SEQ ID NO:19); Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met (SEQ ID NO:20); Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg (SEQ ID NO:21); Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg (SEQ ID NO:22); and Arg-Pro-Lys-Pro-Leu-Ala-Nva-Trp (SEQ ID NO:23).

57. (Currently Amended) An angiogenesis inhibitor compound selected from the group consisting of

~~N-Carbamoyl-Gly-Arg-Gly-Asp-Ser-Pro-(3R,4S,5S,6R)-5-methoxy-4-[(2R,3R)-2-methyl-3-(3-methyl-butyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

~~N-Carbamoyl-GlyArgGlyAspTyr(OMe)ArgGlu (3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl butyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yl ester;~~

~~N-Carbamoyl-GlyArgGlyAsp (3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl butyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yl ester;~~

~~N-Carbamoyl-GlyArgGlyAsp (3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl but-2-enyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yl ester;~~

~~N-Carbamoyl-GlyArg {3-amino-3(pyridyl)} propionic acid (3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl but-2-enyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yl ester;~~

~~N-Carbamoyl-GlyProLeuGly (3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl but-2-enyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yl ester;~~

~~Ac ProLeuMetTrpAla (2R {(3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl but-2-enyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yloxycarbonyl} amino 3 methyl butanol) ester;~~

~~Ac ProLeuGlyMet (2R {(3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl but-2-enyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yloxycarbonyl} amino 3 methyl butanol) ester;~~

~~Ac ProLeuGlyMetAla 2R {(3R,4S,5S,6R) 5 methoxy 4 [(2R,3R) 2-methyl 3 (3 methyl but-2-enyl) oxiranyl] 1 oxa spiro[2.5]oct-6-yloxycarbonyl} amino 3 methyl butanol) ester;~~

~~{2-Methyl-1-[methyl-(1-methyl-piperidin-4-yl)-carbamoyl]-propyl}-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

~~[1-(2-Dimethylamino-ethylcarbamoyl)-2-methyl-propyl]-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

{1-[(2-Dimethylamino-ethyl)-methyl-carbamoyl]-2-methyl-propyl}-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

[1-(3-Dimethylamino-propylcarbamoyl)-2-methyl-propyl]-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

[1-(3-Dimethylamino-2,2-dimethyl-propylcarbamoyl)-2-methyl-propyl]-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

[2-Methyl-1-(4-methyl-piperazine-1-carbonyl)-propyl]-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

{2-Methyl-1-[2-(1-methyl-pyrrolidin-2-yl)-ethylcarbamoyl]-propyl}-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

[2-Methyl-1-(4-pyrrolidin-1-yl-piperidine-1-carbonyl)-propyl]-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester; and

[1-(4-Benzyl-piperazine-1-carbonyl)-2-methyl-propyl]-carbamic acid 5-methoxy-4-[2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester.

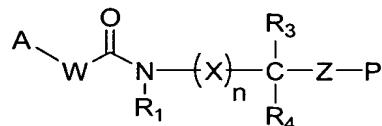
58. (Cancelled)

59. (Cancelled)

60. (Cancelled)

61. (Cancelled)

62. (Currently Amended) A method of treating an angiogenic disease in a subject, comprising administering to the subject a therapeutically effective amount of an angiogenesis inhibitor compound comprising the structure



wherein

A is a Met-AP2 inhibitory core;

W is O or NR₂;

R₁ and R₂ are each, independently, hydrogen or alkyl;

X is alkylene or substituted alkylene;

n is 0 or 1;

R₃ and R₄ are each, independently, ~~hydrogen~~, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; or R₃ and R₄, together with the carbon atom to which they are attached, form a carbocyclic or heterocyclic group; or R₃ and R₄ together form an alkylene group;

Z is -C(O)-, alkylene or alkylene-C(O)-; and

P is a peptide comprising from 1 to about 100 amino acid residues attached at its amino terminus to Z or a group OR₅ or N(R₆)R₇, wherein

R₅, R₆ and R₇ are each, independently, hydrogen, alkyl, substituted alkyl, azacycloalkyl or substituted azacycloalkyl; or R₆ and R₇, together with the nitrogen atom to which they are attached, form a substituted or unsubstituted heterocyclic ring structure;

or

Z is -O-, -NR₈-, alkylene-O- or alkylene-NR₈-, where R₈ is hydrogen or alkyl; and

P is hydrogen or a peptide consisting of from 1 to about 100 amino acid residues attached at its carboxy terminus to Z; wherein

the N-terminus of the peptide is -NR₂R₃, wherein R₂ is hydrogen, alkyl or arylalkyl and R₃ is hydrogen, alkyl, arylalkyl or acyl.

63. (Original) The method of claim 62, wherein said angiogenic disease is an autoimmune disease.

64. (Original) The method of claim 63, wherein said autoimmune disease is rheumatoid arthritis.

65. (Original) The method of claim 62, wherein said angiogenic disease is cancer.

66. (New) The compound of claim 1, wherein R₁ is a substituted or unsubstituted alkyl group.

67. (New) The compound of claim 66, wherein R₁ is a substituted or unsubstituted normal, branched or cyclic C₁-C₆ alkyl group.

68. (New) The compound of claim 67, wherein R₁ is a normal or branched C₁-C₄ alkyl group.